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The Environmental Chemistry of N-Nitroso Compounds

Eco-Control, Inc, Cambridge, Mass

Prepared for

Environmental Protection Agency, Washington, D C Office of Water Supply

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FINAL REPORT

THE ENVIRONMENTAL CHEMISTRY OF N-NITROSO COMPOUNDS

September 3, 1976

Submitted to:

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1.0 INTRODUCTION

1.1 Aims and Objectives

The aims and objectives of this study are as follows:

1) To identify natural and anthropogenic nitrosamines and nitrosamine precursors likely to be found in water;
2) To review the conditions of formation and decomposition of nitrosamine precursors in water, including pH, concentration effects, solubilities, volatilities, amine basicity, kinetics of reaction, photochemical and thermal stability, catalysis by thiocyanate, carbonyls, sulfhydryls or other substances, reactions in presence of inhibitors such as ascorbate and glutathione;
3) To review the formation of nitrosamines and precursors via biological action including biofixation, microbial/bacterial action (*E. coli*, *streptococcus fecalis*), biodegradability;
4) To review the chemistry in water of nitrosamine and precursor formation and decomposition: secondary and tertiary amines or other compound types from natural and industrial sources (amino acids, purines, pyrimidines, ureas, quaternary ammonium compounds, carbamates, guanidines, atrazine, carbaryl, etc.) and effects of nitrates, nitrites, HNO_2, HNO_3, HCN, SO_2, NO, NO_2, N_2O, etc.;
5) To review persistence and fate of nitrosamines in water treatment plants and parallel hazards, if any, generated by the chemical interactions of nitrosamines with chemicals used in water treatment technologies or with other common pollutants;
6) To assess the analytical methods for nitrosamines and precursors

in water; sampling methods, etc. and to suggest procedural changes.

1.2 Methodology

Data on the various N-nitroso compounds of interest was collected from the following sources, in part by computerized searches via DIALOG and MEDLINE/TOXLINE:

a) Primary sources

1. Chemical Abstracts, 1940-present
2. Biological Abstracts, 1960-present
3. Environmental Mutagen Information Center Data Base
4. TOXLINE Data Base
5. Toxicology Information Response Center's Library and Files
6. Index Medicus (partial searches, 1965-present)

b) Secondary sources

1. U.S. Public Health Service Survey of compounds which have been tested for carcinogenic activity
2. Industrial Hygiene and Toxicology
3. Handbook of Toxicology
4. Handbook of Experimental Pharmacology, Vol. XXVIII/2, Chaps. 35-58
5. Clinical Toxicology of Commercial Products
6. U.S. Public Health Service. The Toxic Substances List (1973 Edition).
7. Toxicity of Power Plant Chemicals
8. NAS Blue Book

9. EPA Water Quality Criteria

10. All pertinent chemistry and biochemistry textbooks at the Biology and Chemistry departmental libraries at Harvard University and at the Massachusetts Institute of Technology.

2.0 CHEMICAL SYNTHESIS OF NITROSAMINES

2.1 Introduction

The research literature on the chemical synthesis of nitrosamines and related N-nitroso compounds (such as nitrosamides, nitroso-ureas, etc.) has been reviewed thoroughly by Smith, 1966(S); Butler, 1975(B); Mirvish, 1975(M), 1975a(Ma); and Wolfe, 1976(W). Little can be added to the substance of these reviews, but for purposes of this report the information contained in them is summarized in the following sections and tables along with chemical information taken from sources not reviewed by the aforementioned authors. Secondary references which have been taken from these reviews are not cited in the bibliography but are given in the text as Journal citations preceeded by a letter code--S, B, M, Ma or W--of the review from which they were taken.

2.2 Nitrosation with Nitrite

2.2.1 Synthetic Route

Secondary nitrosamines are prepared by treatment of secondary amines with sodium nitrite and an excess of dilute acid, usually with moderate warming. Water is the solvent. Nitrosamides, nitroso-ureas, nitrosocarbamates and N-nitroso analogues of heterocyclic amines including pesticides are similarly prepared as shown in Table 2.1.

The nitrite mediated nitrosation of more complex 5 and 6 member ring amino-heterocyclic compounds, such as triazoles, thiadiazoles, diazines, triazines, purines and pyrimidines, is also known to occur but in low yield as a side reaction to diazotization (Butler, 1975).

Table 2.1

Nitrosation with NO_2^- in Aqueous Acid

Reaction Type	Citation	Review Source
A) $R_2NH + NaNO_2 \xrightarrow[\sim 60°]{\text{dil. HCl}} R_2N\text{-}NO$ (amines) (60-95%)	Chem. Ber. 95: 1571 (1962)	S
	J. Chem. Soc., 4226 (1961)	S
	Ibid., 846 (1963)	S
R = alkyl, cycloalkyl, aryl, aralkyl and combinations	J. Nat. Canc. Inst. 44: 633 (1970)	W
	Russ. Chem. Rev. 40: 34 (1971)	Ma
	Canc. Res. 34: 1079 (1974)	Ma
	Chem. Rev. 59: 79 (1959)	Ma
B) $R_2NHCR \longrightarrow R_2NC\text{-}R$ (O; NO) (amides)	Org. Syn. II (coll.), 464 (1943)	S
	Ibid., IV (coll.), 780 (1963)	S
	J. Nat. Canc. Inst. 46: 1183 (1971)	Ma
C) $R_2N\text{-}N(H)\text{-}R \longrightarrow R_2N\text{-}N(NO)\text{-}R$ (hydrazines)	J. Org. Chem. 28: 2508 (1963)	S
	Ibid., 29: 311 (1964)	S
	Ann. 376: 239 (1910)	S
	Helv. Chim. Acta 42: 739 (1959)	S

Table 2.1, continued

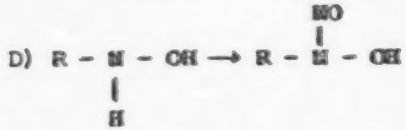
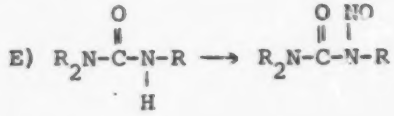
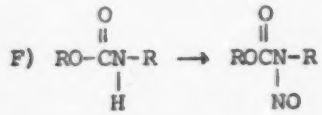
Reaction Type	Citation	Review Source
D)  (hydroxyl amines)	Ann. 263: 175 (1891)	S
	Ibid. 278: 359 (1894)	S
	Ber. 27: 1548 (1894)	S
E)  (ureas)	J. Nat. Canc. Inst. 46: 1183 (1971)	Ma
	Int. J. Cancer 7: 249 (1971)	Ma
F)  (carbamates)	J. Nat. Canc. Inst. 46: 1183 (1971)	Ma
G) Guanidines → N-Nitrosoguanidines	J. Nat. Canc. Inst. 46: 1183 (1971)	Ma
H) Amino acids → N-Nitrosoaminoacids	J. Nat. Canc. Inst. 51: 1833 (1973)	Ma
I) Lecithin → N-Nitroso derivatives	Z. Lebens. Forsch. 151: 52 (1973) Pensabene, 1975	Ma
J) Quaternary ammonium salts → dialkylamino-N-nitrosamines	Nature 236: 307 (1972)	Ma

Table 2.1, continued

Reaction Type	Citation	Review Source
K) Agricultural chemicals → N-Nitroso derivatives	Food. Cosmet. Tox. 11: 807 (1973)	Na, W
L) Drugs and pharmaceuticals → N-Nitroso derivatives	J. Heterocyclic Chem. 11: 619 (1974)	Ma
	Nature 239: 165 (1972)	Ma
M) Amino Heterocyclic compounds → N-Nitroso derivatives	J. Chem. Soc., 1357 (1973)	Ma
	J. Prakt. Chem. 88: 311 (1913)	B
	Ibid. 139: 193 (1934)	B
	J. Org. Chem. 29: 3449 (1964)	B
	J. Prakt. Chem. 134: 282 (1932)	B
	J. Chem. Soc. (1), 1357 (1973)	B
	Chem. Comm., 112 (1970)	B
	J. Chem. 8: 221 (1968)	B
	Chem. Ber. 103: 112 (1970)	B
	Chem. Ber. 29: 2511 (1896)	B
	Ibid. 96: 570 (1963)	B
	Ibid. 91: 1025 (1958)	B
	J. Chem. Soc. (B), 427 (1966)	B
	Giner-Sorolla, et al. (1973)	
N) Proteins → N-Nitroso peptides	Nature 247: 288 (1974)	Ma
	Bonnett (1975)	

2,2,2 Kinetics

In general, the rate of nitrosamine formation is proportional to amine concentration and the square of nitrite concentration at acid pH values in the 2-3 range. The chemical structure of the N-substrate, however, greatly affects the rate constant for this reaction (Mirvish, 1975, 1975a). For example, differences over a $2x10^5$ range have been noted in the nitrosation rates for 15 amines (Table 2.2; Mirvish, 1975) and 21 N-acyl compounds amines (Table 2.3; Mirvish, 1975)

Two generalizations emerge upon analysis of these tables. The data presented in Table 2.2 suggests that ease of nitrosation, as given by k, increases as the basicity (pKa) of the amine decreases. Weakly basic amines, such as morpholine, are much more readily nitrosated than strongly basic ones such as dimethylamine or piperidine. Yet if half-lives of formation ($T_{\frac{1}{2}}$) were to be calculated from these constants, even in the latter two cases, the $T_{\frac{1}{2}}$ would be in the range of several hours. For practical purposes, regardless of kinetics, the nitrosation of amines is a rapid, high yield reaction.

The same can be concluded from Table 2.3, although the kinetics of nitrosation are proportional to the concentrations of amide, nitrite, and H^+. Again the k values are scattered over a $3x10^5$ range, but unlike in the case of amine nitrosation, the nitrosation of amides and related N-acyl compounds cannot be explained by a simple rule. In gross terms the order of ease of nitrosation is urea > carbamate > acyl urea > guanidine > amide.

With regard to the nitrosation of complex heterocycles, less can be said. They are too complex and have not been studied fully. Among

Table 2.2

Rate Constants for the Nitrosation of Amines
(Mirvish, 1975a)

Amine	pKa	k ($M^{-2}Sec^{-1}$)
Piperidine	11.2	0.00045
Dimethylamine	10.72	0.0017
Pyrrolidone	11.27	0.0053
N-Methylethanolamine	9.5	0.010
N-Methylbenzylamine	9.54	0.013
Proline	---	0.037
Sarcosine	---	0.23
Prolylglycine	8.97	0.25
Hydroxyproline	---	0.31
Prolylleucylglycinamide	8.97	0.38
Morpholine	8.7	0.42
Mononitrosopiperazine	6.8	6.7
Aminopyrine	5.04	80
Piperazine	5.57	83
N-Methylaniline	4.85	250

Table 2.3

Rate Constant for Nitrosation of N-Acyl Compounds
(Mirvish, 1975a)

N-Acyl Compound	k
N-Methylbenzamide	0.0014
N-Methylacetamide	0.0025
Dihydrothymine	0.0035
Methylguanidine	0.004
1-Methyl-3-Nitroguanidine	0.008
Dihydrouracil	0.010
Hydantoin	0.042
Ethyl-N-ethyl carbamate	0.10
Hydantoic acid	0.18
Ethyl-N-methyl carbamate	0.37
2-Ureidoethanol	0.38
DL-Citrulline	0.72
Phenylurea	2.2
Ethylurea	3.0
Trimethylurea	7.0
Ethylcyanamide	8.0
Methylurea	10.5
Ethoxyphenylurea	13
Propyleneurea	18
1,3-Dimethylurea	200
Ethyleneurea	400

the various types of heterocyclic amines from which nitrosamines have been isolated, three structural features are recognized which facilitate rapid nitrosation at a rate roughly comparable with the rate of nitrosation of N-methyl-aniline (Boyle, 1975). These are:

1) Electron-withdrawing substituents and electron-withdrawing rings which offer resonance stabilization of the N-nitroso adduct and its dipolar tautomers. The higher azoles offer a case in point.
2) The absence of labile ring protons, which appears to militate against diazotization, favoring nitrosation.
3) Location of the nitrosamine moiety bonded directly to a $\rangle C{=}N-$ unit in the position α to the carbon rather than to a $\rangle C{=}C-$. Furthermore, it should be noted that amino derivatives of five-membered nitrogen heterocycles are weaker bases than those of the six-membered homologous rings; hence, even in dilute acid solution the cyclic $\rangle C{=}N-$ lone pair of the six-membered heterocyclic ring may be considerably more protonated than that of the five-membered ring, affording resonance destabilization and disfavoring nitrosation.

2.2.3 Nitrosation with Reagents Other Than Nitrite

From kinetic studies with aqueous acidic nitrite it has long been known that the nitrous acid formed may be converted to other active nitrosating species, e.g., nitrous anhydride (N_2O_3), nitrosyl thiocyanate (ON-NCS), nitrosyl halide (NOX), or nitrous acidium ion ($H_2NO_2^+$). These nitrosating species derived from nitrite effect N-nitrosation more

rapidly than nitrite itself in dilute acid. N_2O_3 formation is favored as the concentration of water decreases; indeed, this reagent is used primarily to effect nitrosations in acetic acid or in aprotic, anhydrous polar solvents (Smith, 1966), so it is not a significant factor in the chemistry of nitrosamines under aqueous conditions.

Nitrosyl thiocyanate and nitrosyl halides also find application in nitrosations under anhydrous conditions, but unlike N_2O_3, these nitrosating species play an important role in nitrosation of amines present in low concentration in water, and will be discussed in Section 2.3.1.

Organic nitrosylating reagents are commonplace in synthetic chemistry. Although they are unstable in aqueous media, where their formation is also unfavored, they are mentioned here only insofar as they might play a role as nitrosating agents at one of the many water/lipid interphases found in aqueous environments (especially in water contaminated with living organisms). Thus, reaction of nitrous acid, nitrosyl isocyanate, nitrosyl halide and even N_2O_3 with alcohols, phenols and thiols may give rise, respectively, to alkyl nitrites, aryl nitrites, and thio nitrites, which are all highly reactive nitrosating species in non-aqueous environments (Smith, 1966; Mirvish, 1975a; Boyle, 1975).

2.3 Catalytic Nitrosation

Two types of catalytic nitrosation have been documented. One such set of catalysts promotes formation of nitrosating species whose reaction kinetics are faster than those of nitrous acids. The second set allows nitrosation to take place at neutral pH values, under conditions which

otherwise would inhibit nitrosation as described in previous sections.

2.3.1 Effect of Thiocyanate

Boyland and Walker (1974, 1975) and Mirvish (1975) have noted the catalytic effect of thiocyanate, particularly when nitrite concentrations are low. One should recall here that the k for nitrosation of an amine is proportional to the square of the nitrite concentration. In the presence of a 5-10 fold excess of thiocyanate ion (at pH values near 2-3), nitrosyl thiocyanate formation is favored and subsequent amino nitrosation can take place more readily than in the absence of thiocyanate because the k for this type of nitrosation is proportional only to the actual nitrosyl thiocyanate concentration (and but not to its square.

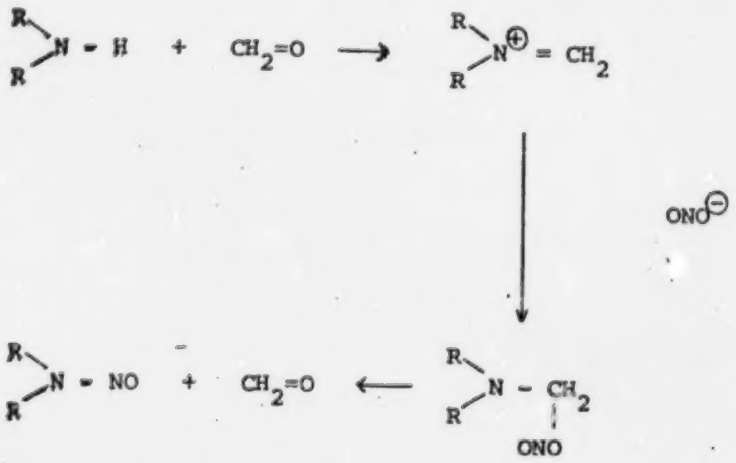
This same reasoning explains the catalytic effect of halogen ions and the more rapid kinetics of nitrosation with nitrosyl halides, but the order of activity is $NCS^- >> Br^-, Cl^-$ (Quart. Rev. Chem. Soc. 15: 418, Ma).

2.3.2 Effect of Aldehydes

Keefer and Roller (1973) showed that formaldehyde and chloral catalyzed the nitrosation of various amines at pH 6-11, under pH conditions well above the pKa of nitrous acid. The reaction takes place because of formation of iminium adducts (amine + aldehyde) which react directly with $NO_2^{\ominus}$ to give transient α-amino methylene nitrites. The latter undergo intramolecular nitrosation to give nitrosamines and the parent aldehyde as shown in Figure 2.1. Presumably other aldehydes, especially those found in biological systems, such as glyoxal, may also catalyze

Figure 2.1

Formaldehyde Catalyzed Nitrosation of
Secondary Amines



this reaction, although none have been found to do so thus far.

Keefer and Roller's work has been substantiated by Marshall (1974). But the latter author found conclusive evidence that nitrite does not react with aldimines (presumably formed in situ by admixture of amines, formaldehyde and biological tissues), except in the presence of water at biological pH values.

2.4 Inhibition of Amine Nitrosation

Agents which effectively lower nitrite concentrations logically can be claimed by kinetic criteria as nitrosation inhibitors. Several inhibitors of this kind have been studied. Fiddler, et al. (1974) and Mirvish (1975a) have demonstrated that ascorbic acid and its isomer erythorbic acid rapidly reduce nitrite under acidic conditions to give nitric oxide, an inert nitrosating species, and the dehydro acid. In vitro and in vivo studies have confirmed that these agents do reduce nitrosamine formation. Gallic acid, tannic acid, hydrosulfite, cysteine, and glutathione show the same mode of action in blocking amine nitrosation. Cantoni and Cattaneo (1974) have suggested further that thiol (R-SH) compounds, including proteins (Bonnett, 1975) may act as sequestrants for nitrite since they react with HONO 10^4 times faster than $R\text{-}NH_2$ groups in gastric juice.

2.5 Miscellaneous Nitrosating Conditions

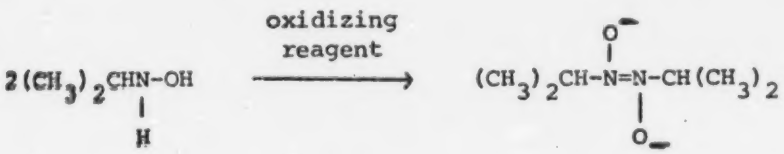
2.5.1 Transnitrosation

Nitroso interchange is known to take place between heterocyclic or aralkyl amines (Buglass, et al., 1973; Mirvish, 1975a). It will be

discussed further in Section 3.

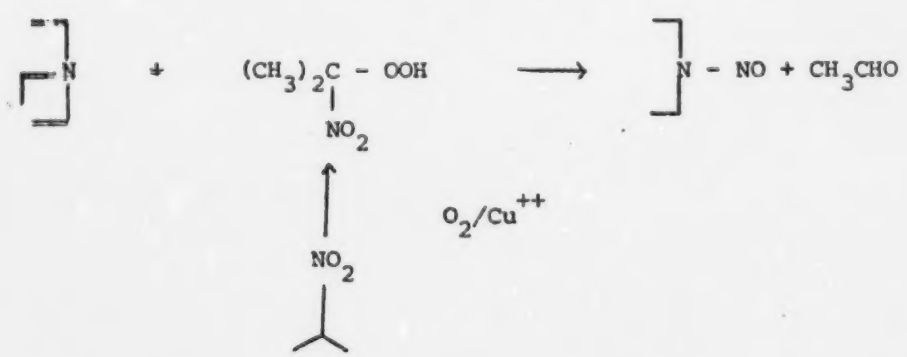
2.5.2 Oxydative Coupling of Hydroxylamines

Maasen and DeBoer (1971) describe the following reaction:



2.5.3 Oxidative Coupling of Nitroalkanes and Trialkylamines

Frank, et al. (1970) describe the following reaction which has gone relatively unnoticed as a possible source of nitrosamines in aqueous environments:



3.0 FORMATION OF N-NITROSO COMPOUNDS IN VIVO AND BY BACTERIA

3.1 Acid Catalyzed Nitrosation in Gastric Juice

The acid catalyzed nitrosation of amines occurs in the stomach contents, which in the case of man, mice, hamsters and dogs, show a pH varying from 1 to 5 during the course of digestion. Long-term feeding studies of amines or amides together with nitrite have substantiated this assertion (Mirvish, 1975; Bicker and Osske, 1974).

Lane and Bailey (1973), for example, found that incubation of 100 ppm dimethylamine (DMA) with nitrite in human gastric juice produced 9.34 ppt concentrations of dimethylnitrosamine (DMNA) after a brief period of incubation at pH 2.5. Schweinsberg (1975) noted further that in vivo nitrosation of DMA in rats follows 1st order kinetics with respect to amine concentration and second order kinetics for NO_2^- concentration as predicted from in vitro chemical kinetic studies. He also confirmed that SCN^- catalyzes nitrosamine formation, the same as in vitro. Mirvish (1975) has reviewed twenty studies in vitro, using a variety of substrates. In all cases endogenous nitrosamine formation was conclusively demonstrated.

One significant difference between the in vitro and in vivo experiments is the yield of the isolated nitrosamines. In each case far less than the amount expected on kinetic grounds alone was isolated, but sufficient to warrant alarm.

Based on the information contained in studies cited here, and by extrapolation from the evidence presented in Section 2, one can conclude that all N-substrates known to be nitrosated <u>in vitro</u> by nitrite and its congeners can take place in vivo under dilute concentration conditions.

By the same token, all reactions known to inhibit nitrosation in vitro can also do so in vivo (Mirvish, 1975).

3.2 Nitrosation in Saliva

In addition to the gastric environment (and other hyperacid environments such as the infected bladder), nitrosamine biosynthesis occurs in hypoacidic environments. Bacteria in human saliva convert nitrate into nitrite via nitrate reductase and further catalyze amine nitrosation by a mechanism akin to aldehyde catalysis, discussed in Section 2.3.2. The work of Ishiwata, et al. (1975); Tannenbaum, et al. (1974); and Wishnok and Tannenbaum (1976) should be consulted for more ample documentation of this phenomenon. Schweinberg (1975) further suggests that thiocyanate may also catalyze amine nitrosation in saliva.

3.3 Nitrosation by Microorganisms at Large

Several studies have proven that microorganisms catalyze nitrosation of amines at neutral pH values, either by direct enzymatic action, by producing secondary metabolites which function as catalysts (like thiocyanate and formaldehyde). Ayanaba (1973) showed that *E. coli*, *S. epidermis*, the fungal hyphae of *A. oryzae* and other bacteria and fungi deaminate trialkyl amines and nitrosate the resulting dialkylamines in the presence of nitrate or nitrite at pH 7.5. Soluble enzymes extracted from homogenates of these organisms produced the same result. In later studies Ayanaba (1973a, b) found nitrosations via microorganisms to occur in acid soil and acid sewage as well. Weaver (1975) reviews this subject in his recent report.

4.0 REACTIONS OF NITROSAMINES

4.1 Introduction

Nitrosamines undergo many reactions which are of interest to synthetic and environmental chemists. Table 4.1 outlines the reactions of synthetic utility and each of the following sections in 4.2 is devoted to establishing the significance of these reactions from the point of view of environmental chemistry. Section 4.3 discusses the chemical stability of nitrosamines together with reactions of no synthetic utility, and 4.4 discusses their environmental stability. The citations in Table 4.1 are taken from Seebach and Enders, 1975 (SE) or Smith (1965) unless otherwise indicated.

4.2 Nitrosamine Reactions

4.2.1 Denitrosation

Nitrosamines are readily denitrosated in nearly quantitative yield to the parent amines. Seebach and Enders (1975) recommend gaseous HCl/Benzene, HBr/HOAc, Raney nickel or transition metal carbonyl compounds as the denitrosation reagents. Williams (1975) reports that iodine in the presence of a nitrite scavenger (NH_2-SO_3H, urea, NH_2OH, NH_3 or hydrazine) rapidly denitrosates nitrosamines in aqueous solution. Challis and Jones (1974) and Hirao, et al. (1973) have denitrosated nitrosamides by acid catalyzed SN_2 displacement. Klus and Kuhn (1972) employed $TiCl_3$ for this purpose, and Baldwin (1971) used metal hydrides.

Acid catalyzed denitrosations are the most reliable. They proceed via protonation of the N-nitroso substrate to liberate the parent amine and an equilibrium concentration of HNO_2. The latter is reduced by one

Table 4.1

Nitrosamine Reactions

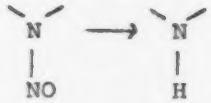
Type	Reaction	Citation	Review Source
A) Denitrosation		Russ. Chem. Rev. 40: 34 (1971)	SE
		Helv. Chim. Acta 47: 166 (1964)	SE
		Aust. J. Chem. 22: 2451 (1969)	SE
		Ann. 765: 78 (1972)	SE
		Arzneim F. 20: 1513 (1970)	SE
		J.A.C.S. 73: 93 (1951)	SE
		Ibid. 79: 2215 (1957)	SE
		Can J. Chem. 48: 1543 (1970)	SE
		Organometal Chem. Synth. 1: 69 (1970/71)	SE
		Tet. Lett. 1971: 3567 (1971)	SE
		Chow (1973)	
		Z. Anal. Chem. 206: 344 (1966)	SE
		Acta. Chem. Scand. 11: 990 (1957)	SE
		J. Chem. Soc. 585 (1929)	S
		Ibid, 711 (1932)	S
		Ann. 151: 366 (1869)	S
		Rec. Trav. Chim. 31: 193 (1912)	S
		J. Org. Chem. 23: 1595 (1958)	S

Table 4.1, continued

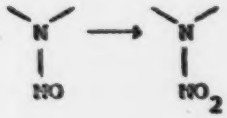
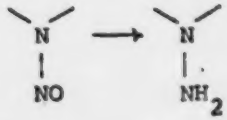
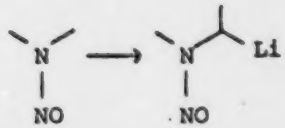
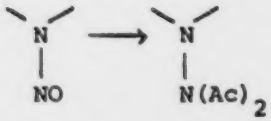
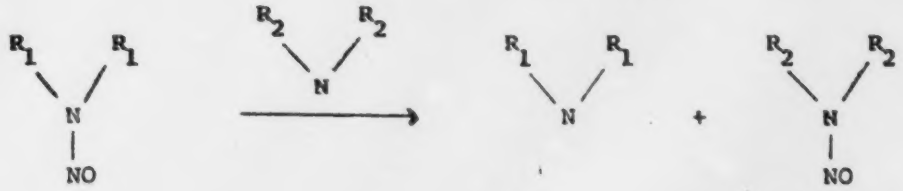
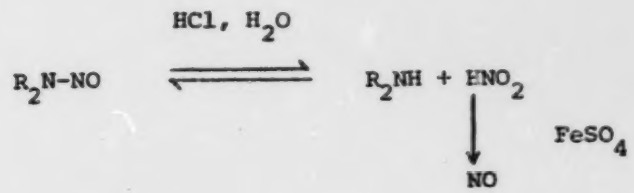
Type	Reaction	Citation	Review Source
B) Oxidation		J. Chem. Soc. 2391 (1954)	SE
		Ibid, 3997 (1955)	SE
		Ibid, 921 (1956)	SE
		Ibid, 1797 (1961)	SE
		Quart. Rev. Chem. Soc. 5: 75 (1951)	SE
		J.A.C.S. 76: 3468 (1954)	SE
C) Reduction (excluding reductive denitrosation)		Russ. Chem. Rev. 40: 34 (1971)	SE
		Ann. Chem. 686: 92 (1965)	SE
		Ibid, 665: 144 (1963)	S
		Org. Syn. (coll.) II, 211 (1943)	S
		J.A.C.S. 74: 3693 (1952)	S
D) Lithiation		Seebach and Enders (1975)	
		Seebach, et al. (1973)	
E) N-alkylation		Gough, et al. (1975)	

Table 4.1, continued

Type	Reaction	Citation	Review Source
F) Transnitrosation		Buglass, et al. (1973) Kirvish (1975a)	

of the components of the reaction medium, thus driving the reaction to completion. Smith (1976, p. 473) cites the following representative example of the denitrosation mechanism in acid:



Note should be made between this mechanism of denitrosation and the mechanism of inhibition by ascorbate in nitrosamine formation (Section 2.4).

Denitrosation may also take place via direct reduction with metals such as zinc or sodium, Raney nickel and metal carbonyls and is widely applicable in the denitrosation of nitrosamines, nitrosamides, nitrosimines, nitrosoureas and nitrosourethanes to the parent N-compound.

4.2.2 Oxidation

Secondary nitrosamines are oxidized to nitramines in good yield with peroxide reagents or nitric acid. Castegnaro, et al. (1972) obtained nearly quantitative yield by oxidation of nitrosamines in 60/40 H_2O/ACOH with 2-butanone peroxide. Similar results were obtained by Tolstikev, et al. (1971) with t-amylhydroperoxide with $MoCl_5$ as catalyst. This type of oxidative transformation has not been studied in the case of N-acyl-N-nitrosamines.

4.2.3 Reduction

Reduction of nitrosamines in general takes two principal courses. Reductive denitrosation has been discussed in 4.2.1 above. Reduction of both primary and secondary nitrosamines to hydrazines can generally be accomplished with zinc in acetic acid or with LAH in tetrahydrofuran (Smith, 1966, p. 478). Belyaev, et al. (1973) suggest that hydrazine and/or diimide in aqueous solution can also effect the reduction of nitrosamines to hydrazines.

A drawback to chemical reductions of the kind just discussed lies in the intrinsic reduction mechanism. The reaction must be controlled or else over-reduction, manifested by reductive denitrosation will take place. The problem is obviated by reverting to controlled potential electrochemical reduction. This technique is particularly suited to reduction of trace amounts of N-nitroso compounds in water (Nikulin and Klochkover, 1972, 1973; Iversen, 1971; Dorn, et al., 1966) and has recently been adapted as an adjunct to the microanalytical determination of nitrosamines (see Section 6 and papers by Osteryoung, 1976).

4.2.4 Lithiation

The metalation of nitrosamines in general had given unsatisfactory results until Seebach and Enders discovered that lithium diisopropyl amide cleanly metalated the α-position of nitrosamines. The α-lithio derivative in turn can be alkylated in high yield with carbonyl derivatives or benzyl bromides. Thus, α-lithiation and concomitant alkylation may find application as a novel method for trapping nitrosamines and derivatizing prior to qualitative or quantitative analysis. The synthetic utility of

this reaction is amply discussed by the authors in their 1975 review.

4.2.5 Acylation

Heptafluorobutyric anhydride reacts with nitrosamines to give N-bis acyl derivatives suitable for gas chromatographic identification. This is the only reported instance of the reaction of acylating reagents with nitrosamines which occur in nearly quantitative yield (Gough, et al., 1975).

4.2.6 Transnitrosation

Transnitrosation represents a group of reactions of minor synthetic importance. It is useful in the preparation of heterocyclic nitrosamines (Butler, 1975), aryl and aralkyl nitrosamines (Buglass, et al., 1973; Mirvish, 1975a, p. 333) which otherwise would not form readily by direct nitrosation. The scope of transnitrosation conditions has not been studied fully and may be wider than expected, especially among the more complex heterocyclic nitrosamines.

4.3 Chemical Stability of Nitrosamines

In addition to the defined set of reactions described in the preceeding sections, nitrosamines undergo additional transformations to yield heterogeneous end products. Many of the reactions which will be discussed here are autolytic and relate to the thermal and photochemical stability of N-nitroso compounds.

4.3.1 Decomposition at Alkaline pH

Smith (1966, p. 474) reports that simple nitrosamines, both alkyl and cycloalkyl, are not at all readily attacked by bases, apart from the conversion to primary nitrosamine salts (a fact which is used to advantage in the extraction of simple nitrosamines for quantitative analysis; see Section 6). N-alkyl-N-nitroso amides and N-nitrosoureas, by contrast, react readily with base to give alkyl diazotates which decompose spontaneously to give diazoalkanes (Challis and Jones, 1975; Hecht and Kozarich, 1973).

In this connection, Hassner and Reuss (1974) demonstrated the facility with which N-nitrosocarbamates are converted into transient diazoalkanes in the presence of mild base. The intermediate diazoalkanes rapidly rearrange to vinyl ethers and to olefinic fragments of various composition. N-Nitrosamines similarly fall apart to isocyanic acid salts and diazoalkanes. Under specialized conditions, these diazoalkanes produced after base decomposition of N-nitroso compounds react with acetyl donors to give acetates and N_2 gas.

The prevalent theory regarding the carcinogenicity of N-nitroso compounds is posited on the premise that under biological conditions all such compounds are degraded by enzymatic methods similar in mechanism to basic hydrolysis to form diazoalkanes. The latter are potent nucleic acid alkylators and therefore mutagens.

4.3.2 Thermal Stability

The thermal stability of nitrosamines has not been studied in detail per se. Under neutral pH conditions or in the solid state the

thermal stability of these compounds has been considered only in connection with the reaction conditions to which the nitrosamines may be subjected, such as acid or base hydrolysis, as discussed in preceeding sections, or in the presence of light (Section 4.3.3).

Circumstancial evidence suggests that simple, alkyl amino nitrosamines are sufficiently temperature stable to withstand GLC conditions (Brooks, 1972b Cox, 1973; Fine, all citations), but they do pyrolize at elevated temperatures to give nitrosyl radicals. Fine (1975c and accompanying references) has relied upon this phenomenon for the development of a thermal energy analyzer. Nitrosyl radicals resulting from the pyrolysis of N-nitroso piperidine and pyrrolidine have also been used as a means to inhibit styrene and chloroprene popcorn polymerization (Yamamoto and Nishihara, 1974; Oshima, et al., 1972) and as inhibiters or initiators in other free radical reactions (Minisci, 1973).

More complex, heterocyclic nitrosamines pyrolyse readily, some even at or below ambient temperature. In the course of studies on nitrosamine formation, Wolfe (1976) found that N-nitroso atrazine reverts to atrazine under normal GLC conditions. Butler (1975) suggests in his review that N-nitroso derivatives of heterocyclic amines which do not possess the structural, stabilizing features, described in Section 2.2.2 (last paragraph) readily undergo thermolysis in a Gomberg-Bachmann type reaction.

Smith (1966, p. 470) reports that N-alkyl-nitrosoamides thermolyze at 20-100°C to give either an ester or an acid and an olefin. N-nitroso-N-methyl urea decomposes slowly at ambient temperature and rapidly at 30°C to methyl isocyanate, nitrogen and water (Smith, 1966, p. 472). Pre-thermol decomposition of acrylarylnitrosamines has been studied by Cadogan (1941).

4.3.3 Photolysis

The photolysis of nitrosamines has been reviewed by Chow (1973). Gas phase photolysis of alkyl nitrosamines gives nitric oxide and products to be expected from the disproportionation of dialkylamino radicals. N-nitroso dimethylamine decomposed in sunlight with a half-life of 30 minutes (Hanst, et al., 1976).

Photolability in solution is directly related to the dipolar character of individual N-nitroso compounds, and the latter are enhanced in the presence of H^+, Lewis Acids, and certain cations. The primary photoproduct in 0.1 to 0.001N HCl is an aminium ($R_2NH\cdot^+$) radical. The k of formation ranges between 10^4 and 10^7 $M^{-1}sec^{-1}$. Aminium radicals in turn can react in three ways: disproportionation, photoreduction, and photoaddition, as exemplified in Figure 4.2, which depicts the photochemical behavior of N-nitroso pyrrolidine. The rates for reactions 2, 3 and 4 are significantly faster than for reaction 1. Bendall, et al. (1972) and Burns and Alliston (1971) describe these reactions in greater detail.

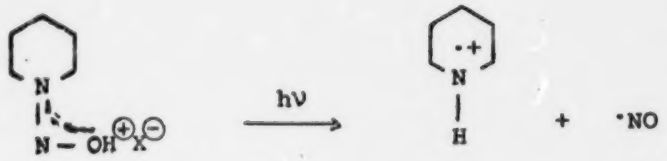
Chow (1973) also reviews the photolysis of N-acyl-N-nitroso compounds, which undergo related photolytic transformations.

4.3.4 Radiolysis

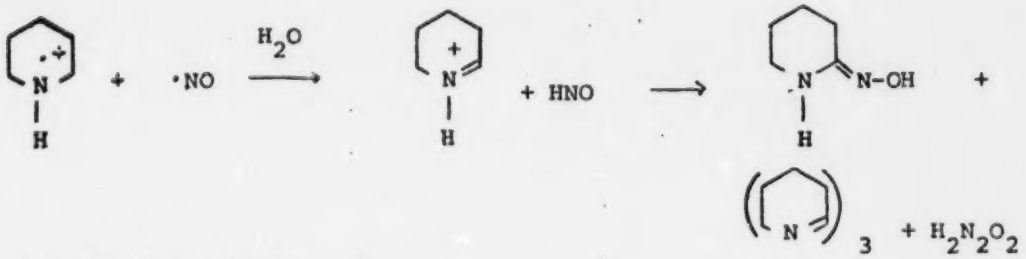
Gamma radiation at a rate of 0.3 to 6.0 Mrads of cobalt effected instantaneous radiolysis of dimethyl nitrosamine (100 ppm in water) to give dimethyl amine and dimethyl nitramine (Hirano, 1972). The mechanism of nitrosamine radiolysis has not been fully studied.

Figure 4.2

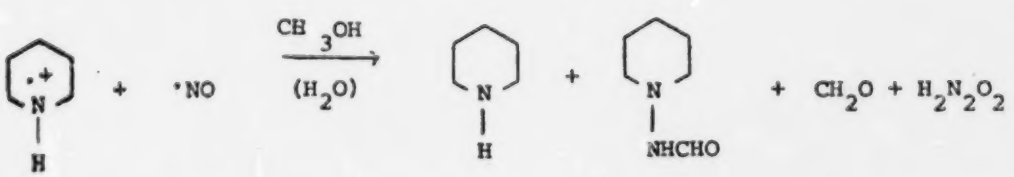
Photolysis (Reaction 1)



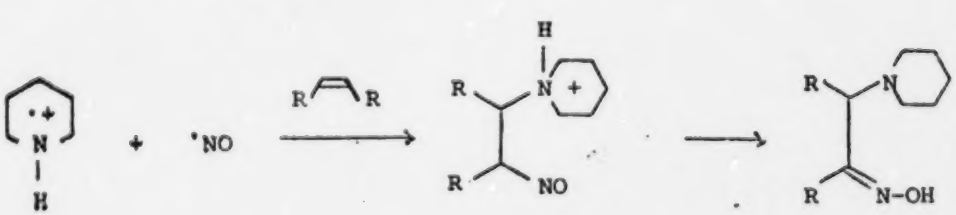
Disproportionation (Reaction 2)



Photoreduction (Reaction 3)



Photoaddition (Reaction 4)



4.4 Environmental Stability of Nitrosamines

Factors which are secondary to the intrinsic stability of N-nitroso compounds further determine their environmental stability and persistance. These are described in Sections 4.4.1 and 4.4.2.

4.4.1 Degradation in Aquatic Environments

Although the technical literature on the subject is scanty, there is significant disagreement on the role played by aquatic organisms in decomposing N-nitroso compounds. Sander, et al. (1974) suggested that bacterial floras in sewage treatment plants remove nitrosamines, derived from simple alkylamines, found in the influent waters. In disagreement, Tate and Alexander (1975) marshalled evidence suggesting that the same kinds of nitrosamines are not degraded in eutrophied lake waters even over a three month period. The authors found further that nitrosamines disappear from soil only after a 30 day induction period. Nitrosamine degradation in sewage showed a $T_{\frac{1}{2}}$ of 14 days. A third opinion emerges from Sander, et al. (1975) who found that cress plant blooms metabolize the nitrosamines of diethylamine, morpholine and piperazine, which are taken up from the environment. Thus, at present, the course of nitrosamine degradation in the aquatic environment at large remains to be elucidated.

4.4.2 Metabolism by Higher Organisms

More conclusive information emerges from whole animal and in vitro studies on the metabolism of N-nitroso compounds in mammals. Microsomal enzymes offer the principal but not the sole route to nitrosamine

inactivation (Lake, 1974a, b; Heading, et al., 1974). Three metabolic pathways intimately related to the microsomal oxidase enzyme complexes have been studied, so that the following inferences can be drawn:

a) N-nitroso compounds are partially N-demethylated and the desmethyl products rearranged to diazoalkanes which in turn are "inactivated" in the course of effecting mutagenic biological (irreversible) alkylations (Magee, 1975; Krueger, 1971).

b) N-nitroso compounds are partially hydroxylated by microsomal hydroxylases (similar to the steroid hydroxylases) and the hydroxy groups then are conjugated and excreted (Bartsch, et al., 1975; Krueger and Bertram, 1975; Mortesano and Magee, 1974; Grandjean, 1976, Gessner, 1976).

c) N-nitroso compounds are also partially hydroxylated to intermediates which serve as substrates for catalase or alcohol dehydrogenase to give formaldehyde and other aldehydes as end product metabolites (Phillips, 1974).

In sum, it is generally agreed that N-nitroso compounds, particularly the nitrosamines, are metabolized by higher mammals. The rate of metabolism and the pathway are not fully known.

5.0 Occurrence of N-Nitroso Compounds and Their Precursors in the Environment

5.1 Nitrosamines in Water and Air

The carcinogenic potential of nitrosamines (Shapley, 1976; Mirvish, 1975) both as byproducts of cigarette smoking and as contaminants in food and water sources has prompted numerous investigations of their environmental distribution. Fine, et al. (1975d) should be consulted for a general review of nitrosamine distribution in water and in air. This study reports the findings of studies on New Orleans' drinking water, which contained as many as 24 N-nitroso compounds (including N-nitroso pesticide derivatives) in the 0.1 ppb range. Thermo Electron Corporation's (1975) study of water near amine production facilities (Belle, Virginia) uncovered levels of 2-4 ppb dimethyl nitrosamine. Water treatment plant effluents in the same region were found to contain 3-9 ppb by part of a parallel study conducted by DuPont (1975).

Sander (1973) reviews the environmental and epidemiological impact of nitrosamines, nitrate, nitrite and amines in water.

The distribution of nitrosamines (volatile) in air is discussed in several recent reports (Fine, 1976; Thermo Electron Corporation, Report, 1975; Pellizzari, 1976; and DuPont, 1975). Significant concentrations of airborne nitrosamines were found in the vicinity of industrial sites for dimethyl amine and dimethyl hydrazine production. The following is a typical finding: dimethyl nitrosamine occurs in concentrations of 0.02 to 0.96 ppb in the vicinity of Baltimore, Maryland, and in 0.014 to 0.051 ppb near Belle, West Virginia. Waltham, Massachusetts, which is not situated in an industrial area where amines are being produced, had no detectable nitrosamine concentration. In New York City,

an air sample taken on the road, two miles east of the George Washington Parkway, was shown to contain dimethyl nitrosamine at a concentration greater than 8 ppt (Thermo Electron Corporation, 1975).

5.2 Nitrosamines in Food

Mirvish (1975, 1975a) has authoritatively reviewed the occurrence and hazard of nitrosamines in food. Cured foods represent the most widely recognized potential dietary source of nitrosamines. The epidemiological significance of this dietary source, along with extensive statistics on the dietary intake of nitrite and nitrate, are discussed by White (1975), Sen, et al. (1974), and Sakai and coworkers (1971). Other citations on this subject are summarized by Tannenbaum (1974), and Singer and Lijinsky (1976a and b).

5.3 Nitrosamine Precursors

The chemical ecology of nitrosamine precursors has not been subjected to definitive review. Attention of the reader is called to papers by Singer and Lijinsky (1976a), Mirvish (1975a), Weaver (1975), and Sander (1973). The conclusions to be drawn here by way of summary are as follows:

a) Nitrosamine precursors are ubiquitous. Secondary amine precursors enter the environment either as industrial waste products or as secondary metabolites from a variety of organisms. More complex N-substrates, such as pesticides, also provide a ready source of candidates for nitrosation.

b) Nitrite enters the environment via nitrate or ammonia, both substrates for biochemical conversion to nitrite. Nitrite can also be viewed as a byproduct of the food processing industry.

c) Even in the absence of classical nitrosating conditions, nitrosamines arise via catalytic chemical or enzymatic conversion. The catalysts--aldehydes, thiocyanate, bacterial and fungal-enzymes--are present throughout the eco-system.

One should bear in mind also that N-nitroso compounds are chemically, thermally and photochemically labile. Their synthesis in the environment can be effectively inhibited by agents (reducing agents, SH compounds) which are equally as ubiquitous as the reactants in the nitrosation reaction. Nitrosamine metabolism is commonplace, among higher organisms. The evidence available to date suggests that nitrosamine production is counterbalanced by nitrosamine degradation.

5.4 Potential Externalities Affecting the Nitrosamine Cycle

5.4.1 Effect of Chlorination

The use of chlorination in water treatment technology is widespread. Given that the redox potentials of chlorine, hypochlorite, chlorine-dioxide and related species (see Handbook of Chemistry and Physics), under most alkaline, neutral, or acidic conditions, is greater than the nitrite-nitrate couple's potential (0,94 volts), one can infer with confidence that the half-life of nitrite is small in waters treated with chlorination agents. Insofar as these agents lower nitrite concentrations (by oxidizing nitrite to nitrate), it follows that they should reduce the incidence of

nitrite mediated N-nitrosation.

But the full impact of chlorination on the nitrosamine cycle is not known and it would have an adverse impact if chlorination of untreated effluents were to produce significant quantities of chloral, a known catalyst for nitrosamine formation, or other reactive aldehydes. The observation that chlorination of untreated effluents yields a host of new compounds, including chlorinated heterocyclics, may also be of significance since these compounds, themselves little studied, provide an unpredictable substrate pool for N-nitroso formation.

Increases in the concentration of chloride ion (and also H+) in water as a consequence of chlorination further impinge adversely on nitrosamine chemistry (chloride ion is a nitrosation catalyst, albeit a weak one (Section 2.3.1). Lastly, note should be made that halomethane byproducts of chlorination (chloraform, methylene chloride) are readily metabolized *in vivo* to formaldehyde (Ahmed and Anders, 1976), which is a potent catalyst for *in vivo* nitrosation by nitrite species biologically derived from nitrate.

5.4.2 Effect of Ozonation

Ozone treatment of water in sanitary engineering may equally affect the nitrosamine cycle. Ozonation of tannins, lignins, and other organics found in water leads to aldehyde formation. An increase in the concentration of formaldehyde found in the aquatic environment, as a result of ozonation, would have measurable repercussions on the rate of nitrosamine synthesis. With reference to Section 2.5.2, it is also possible that ozone itself, ozonides or ozone derived lipid peroxides may also catalyze the disporpor-

tionation of nitramines and trialkylamines to give nitrosamines. On the other hand, ozone and its derivatives may mediate the oxidation of nitrosamines to nitramines as in Section 4.4.2. They also can oxidize nitrite to nitrate.

Lastly, ozone is known to excite nitrosyl radicals (Fine, 1975c). The reactivity of these radicals, which could easily be derived from nitrite or nitrate, is sufficiently high to warrant concern in view of the variety of products which arise from nitrosyl radical interactions (Section 4.3.3, Figure 4.2).

6.0 IDENTIFICATION AND QUANTITATION OF NITROSAMINES

6.1 Extractive Procedures

Nitrosamines and related compounds are generally isolated by extractive techniques (Fine, all citations). Volatile N-nitroso compounds are steam distilled, treated with base, extracted in organic solvents and subjected to subsequent analysis (Fine, et al., 1976; Moehler and Hallermayer, 1974; Alliston, 1972; Brooks, 1972b). Kawataba, et al. (1974a and b) submit the organic extracts after steam distillation to TLC clean-up, noting that interfering compounds are removed more effectively in this manner. Vasundhara, et al. (1975) reports additional TLC clean-up conditions.

Non-volatile N-nitroso compounds are extracted out of water into warm mineral oil (Fine, et al., 1970, 1975b) and/or extracted with CH_2Cl_2 (Fine, et al., 1974a). Again base treatment, prior to extraction is frequently used (Cox, 19[illegible]).

Airborne nitrosamines are collected by condensation at low temperature (Fine, 1975d; Thermo Electron Corporation, 1975) or by trapping as the salt in aqueous KOH (DuPont, 1975).

6.2 Separation

Gas liquid chromatography (GLC) is the preferred method for separation of volatile N-nitroso compounds. A large number of liquid phases and column conditions have been tested successfully (Fine, all citations; Bryce and Telling, 1972; Gough and Webb, 1973, 1974; Dure, et al., 1975; Gough and Sawyer, 1975). Fine, et al., (1976) recently introduced high pressure liquid chromatography (HPLC) as an alternative to GLC, on the

grounds that this single technique would afford separation of volatile and non-volatile nitrosamines. Cox (1973) had carried out preliminary studies on HPLC, but only on derivatized nitrosamines.

5." Quantitation - GLC Detectors

Two types of GLC detector have proven superior to flame and thermal ionization detectors in providing sensitivity in the sub part per billion range. Dure, et al. (1975) developed a N-selected flame detector which allows for quantitative detection at the 100 ppb range and qualitative detection at around 25 ppb concentrations, this providing that there are no interfering, unknown compounds in the sample.

Electron capture detection and quantitation is a more widely used technique. Allston (1972) and Eisenbrand (1972) subjected the concentrated pre-cleaned nitrosamine extracts to electrochemical denitrosation. The resulting amines were then derivatized with fluoro-2,4-dinitrobenzene or other electron capturing reagents and submitted to GLC quantitation with a Tritium foil detector. Cox (1973) used a variant of this procedure for his HPLC studies, preferring to quantitate the derivatized nitrosamines spectrophotometrically. Cox's GLC studies were in agreement with those of Allston and Eisenbrand, affording 10-100 ppb sensitivity of detection.

Brooks, et al. (1972) resorted to electron capture detection of the nitrosamines bis-acylated with heptafluorobutyric anhydride (see Section 4.2.5). The authors obtain detection sensitivities of 1 to 4 ppm based upon material injected into their GLC apparatus and overall detection sensitivities of 40-80 ppb based upon original sample weight.

6.4 Quantitation - Mass Spectrometry (MS)

With the advent of combined GLC/MS in recent years, numerous toxicants have been analyzed by this manner, including nitrosamines (Osborne, 1972; Bryce, et al., 1972; Saxby, 1972; Gough and Webb, 1973, 1974). Because the GLC detection procedures described in Section 6.4 are not specific for N-nitroso compounds or their derivatives, confirmation by GLC/mass spectrometry has been mandatory for the identification of unknown compounds whose retention times cannot be matched by any standard.

MS as a detection technique is cumbersome and necessitates scrupulous sample pre-purification and column separation in order not to introduce spurious results. Certainly this is the case when a full double focusing magnetic MS is used as in most of the GC/MS studies on nitrosamines published to date. Moreover, the sensitivity of MS as a detector falls short of expectations, generally in the 100 ppb range.

6.5 Quantitation by Thermal Energy Activation

This technique is described in all citations by Fine and the Thermo Electron Corporation. It is selective for the nitroso group and is sensitive to a narrow range of interfering groups which normally are readily excluded from the nitrosamine fraction. Sensitivity of detection can be as low as the ppt range. Thermal Energy Analyzers, however, are esoteric analytical devices of limited versatility in the analytical laboratory.

6.6 New Techniques Not Explored to Date

The following new techniques have not been applied in the analytical chemistry of nitrosamines, but are under development:

a) Peshkova, et al. (1975) have introduced an extractive technique designed to stabilize N-nitroso compounds. Volatile and non-volatile N-nitroso compounds are trapped in aqueous solution as ion pairs with tributyl-ammonium sulfate. The ion pair readily partitions into chloroform.

b) Portoghese and Larson (1973) developed a selective tritiation procedure for nitrosamines which places the label alpha to the bridgehead nitrogen. Radiochemical identification and quantitation of nitrosamines after chromatography is therefore possible.

c) Osteryoung (1976) has applied microanalytical pulse voltametry to the detection of N-nitroso groups in aqueous solution. The technique is a sensitive potentiometric technique which measures the characteristic reduction wave of N-nitroso compounds to hydrazines. If microanalytical voltametry is applied to preconcentrated samples, detection sensitivities in the ppb range can be achieved.

d) Multiple ion detection or negative ion detection MS units are now available at relatively low cost as replacements for the traditional double focusing MS. Process time is less and the sensitivity of detection higher. If applied in conjunction with HPLC or GLC of nitrosamines, sub-ppb detection limits might be achieved (K. Biemann, personal communication).

7.0 SUMMARY WITH RECOMMENDATIONS

7.1 Formation of N-Nitroso Compounds

Nitrosation in aqueous acid in the presence of nitrite and secondary amine substrates affords high yields of N-nitroso compounds. Under neutral conditions, N-nitroso compound formation results via aldehyde or thiocyanate catalysis.

Many of the reactions whose course has been studied in vitro occur readily in vivo, either in hyper acid environments, such as the gastric system or at physiological pH values in aquatic eco-systems at large in the presence of microorganisms.

Nitrosation reactions are readily inhibited by several classes of molecules, and these inhibitory reactions also take place in vivo.

7.2 Degradation of N-Nitroso Compounds

The ease with which N-nitroso compounds decompose chemically parallels their ease of synthesis. On the average, N-nitroso compounds undergo denitrosation, oxidation, and reduction under many conditions. They are thermally and photochemically unstable and alkali labile. The multiplicity of conditions which afford N-nitroso compound decomposition cannot be explained by simple rubrics or unitary hypotheses.

The photochemical instability of nitrosamines in aquatic environments suggests that on this premise alone they cannot be assumed to be persistent hazards. Both lower and higher organisms also readily metabolize the more ubiquitous types of N-nitroso compounds, the nitrosamines. The pathways for N-nitroso metabolism require further elucidation.

7.3 Distribution in the Eco-system

N-nitroso compound precursors are distributed throughout the eco-system, but the actual universality of N-nitroso compounds, in particular the nitrosamines, is questionable given scanty data on this subject accumulated to date. The kinetics of an ecological "nitrosamine cycle" are not known; the "cycle" itself is poorly understood.

7.4 N-Nitroso Compound Analysis

Analytical techniques for N-nitroso compounds share several common drawbacks. All present techniques are predicated on the assumption that a set of N-nitroso compounds which are in a given sample, when the sample is collected, will be the same set that is detected after the analytical sequence is completed. This assumption can be questioned in the case of all but the simplest nitrosamines on chemical grounds. It is doubtful that all N-nitroso compounds will survive base treatment, steam distillation and GLC (and unintentional photolysis) prior to detection, in view of the considerations raised in Sections 2-4 of this report.

Prudence dictates that base treatment and steam distillation should be avoided as the principal techniques for N-nitroso compound extraction and concentration. The use of macroreticular resins, polyurethane plugs, or ion-exchangers which are commonplace devices in pesticide analysis, should be investigated as an alternative means to effect N-nitroso compound removal from water and concentration prior to analysis.

In future analytical studies it may be necessary to instantaneously derivatize the N-nitroso compounds at the time of collection--either by electrochemical reduction to hydrazines, by electrochemical denitrosation

to amines, by oxidation to nitramines (section 4.2.2) or complexation as stable, lipophilic charged ion pairs.

For routine analyses, GLC/electron capture detection appears to be cost-effective. The use of pulsed Scandium foil detectors (Analog Technology Corporation) instead of tritium foils, together with halogenated derivatives of N-nitroso compounds or of the parent amines, can readily achieve part per trillion detection limits (see Analog Technology Corporation product brochure on Detector ATC Model 140, which reliably detects less than 2×10^{-13} g of lindane).

MS sepctrometry should be further investigated as a detection tool, especially in view of the new technology introduced by Finnegan and Varian for multiple ion or negative ion detection. The projected cost for these types of MS spectrometers in the next four years is under $25,000.

Thermal Energy Activation is the most specific and sensitive device for the detection of N-nitroso compounds. Its ultimate utility in the analytical laboratory, however, is not as great as that of an MS system.

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